PATENT

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**(Case No. 99-849-A)**

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| **In the Application of:** | ) | |
| | ) | |
| **Odile Leroy** | ) | **Examiner: Duffy, P.A.** |
| | ) | |
| **Application No.: 09/423,698** | ) | **Group Art Unit: 1645** |
| | ) | |
| **Filing Date: February 10, 2000** | ) | **Confirmation No.: 7060** |
| | ) | |
| **For: Multivalent Vaccine Composition With Mixed Carrier** | ) | |

## BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The applicants hereby file an original and three copies of this appeal brief.

## I. REAL PARTY IN INTEREST

The real party in interest is Aventis Pasteur SA of Lyon, FRANCE.

## II. RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences.

## III. STATUS OF CLAIMS

Claims 1-24 are pending and rejected, which rejections are appealed from. A clean set of the pending claims, all of which are involved in this appeal, is attached as Appendix A.

## IV. STATUS OF AMENDMENTS

The final office action, mailed February 18, 2004, stated that the amendments filed October 23, 2003, which were made in response to the previous office action, were entered into the record.

However, the applicant received a Notice of Non-Compliant Amendment and subsequently mailed a revised amendment, which included a complete list of pending claims 1-24, on November 25, 2003. The final office action did not indicate whether the revised amendment, made in response to the Notice of Non-Compliant Amendment and mailed November 25, 2003, was entered.

The applicant presumes in this Appeal Brief that its revised amendment to the claims, mailed November 25, 2003, has been entered. Appendix A, which lists the currently pending claims, is identical to the list of claims mailed November 25, 2003 in response to the Notice of Non-Compliant Amendment, and mailed again on April 19, 2004 in response to the final office action. The Advisory Action, mailed July 14, 2004, made no reference to the list of claims submitted in response to the final office action.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

There are two independent claims involved in this appeal: claims 1 and 16. Both independent claims recite pharmaceutical compositions comprising polysaccharide-carrier protein conjugates. Furthermore, the claimed compositions comprise at least two different carrier proteins. The use of not one, but at least two, carrier proteins for the first time solves the problem of "negative interference," which occurs when the maximum load of carrier protein in a conjugate-based vaccine is reached. Negative interference causes a reduced immune response against polysaccharides, and therefore the elimination of negative interference results in a more effective vaccine composition. *See* specification at p. 4, lines 8-18.

The compositions recited in claim 1 comprise polysaccharide derived from *Streptococcus pneumoniae*. As such, they are intended for the treatment and prevention of *Streptococcus pneumoniae* infections, which are found in the severe forms of pneumonia, septicemia, and meningitis. *See* specification at p. 2, lines 13-17. Additionally, the compositions of claim 1 comprise at least two different, unspecified, carrier proteins. In contrast, the compositions recited in claim 16 may comprise polysaccharide derived from any source and as such are intended for the treatment and prevention of a wide range of infections caused by pathogenic agents, including bacteria. Furthermore, the compositions of claim 16 comprise the two carrier proteins diphtheria toxoid (Dt) and tetanus toxoid (Tt).

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-24 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over Chu *et al.*, Infection and Immunity, 40:245-56 (1983) (hereinafter "Chu") in combination with Merck & Co. Inc., European Patent Application No. 0 497 525 A (hereinafter "EP '525"). This ground of rejection has been maintained through the final office action (mailed February 18, 2004) and the Advisory Action (mailed July 14, 2004), and is presented here for review.

## VII. ARGUMENT

The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not establish a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. *See, e.g., In re Rinehart*, 531 F.2d 1048 (CCPA 1976). The *prima facie* case of obviousness is composed of three elements, the first of which is a suggestion or motivation to modify a prior art reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The teaching or suggestion to make the claimed combination must be found in the prior art, and may not be based on the applicant's disclosure. *Id.* In other words, "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016 (CCPA 1972).

### A. Neither Chu nor EP '525, either separately or in combination, teaches or suggests the compositions recited in claims 1-15 and 24

Claim 1 recites a composition comprising at least two different kinds of polysaccharide-carrier protein conjugates, wherein the polysaccharide is derived from *Streptococcus pneumoniae* and wherein the carrier proteins of the conjugates are of at least two different types. Claims 2-15 and 24 are directly or indirectly dependent on claim 1, and therefore they also include these two claim elements. In the cited prior art, Chu fails to teach the second element (polysaccharide derived from *Streptococcus pneumoniae*), and while Chu teaches a composition comprising two carrier proteins, Chu fails to provide any teachings suggesting or motivating the use of two carrier proteins generally. Meanwhile, EP '525 fails to teach the first element (at least two conjugates comprising different carrier proteins). Therefore, to establish a *prima facie* case of obviousness, the Office must show

some suggestion or motivation to combine the teachings of Chu and EP '525 to arrive at the composition recited in claim 1.

The Office has not pointed to any suggestion in Chu to make any additional compositions comprising at least two different kinds of polysaccharide-carrier protein conjugates, wherein the conjugates contain different carrier proteins—much less a suggestion to make such a composition wherein the polysaccharide is derived from *Streptococcus pneumoniae*, as recited in claim 1—nor has the Office identified anything in Chu indicating that there are any advantages in employing different carrier proteins in the same vaccine composition. Chu simply contains no such suggestions. Moreover, the Office has not shown that one of skill in the art would have been motivated to modify the composition taught by Chu to arrive at the composition recited in claim 1. In fact, upon reading the results described in Chu, one of skill in the art would have been discouraged from making any additional compositions comprising at least two different conjugates. This is because Chu's results of experiments with such compositions were actually negative—they failed to elicit a stronger immune response. As stated on page 249, col. 2, lines 8-17:

> The effect of injecting both Hib conjugates [*i.e.*, Hib-TT and Hib-HCH] was similar to that observed with the monovalent preparations. The total Hib polysaccharide dose was 2.5 μg in the mice receiving either the monovalent or the bivalent preparations. There were no differences between the anti-Hib antibodies in the groups that received both Hib conjugates after any of the three immunizations by using the criteria of either the GM or the percentage of responders.

Accordingly, Chu does not suggest that using two different carrier proteins has any beneficial or desirable effect. Indeed, the description of these results in Chu is tantamount to teaching away from making the composition recited in claim 1 as the ordinary artisan would have been discouraged from going to the extra effort of preparing such a composition with the concomitant uncertainties associated with adding extra antigenic components to such a composition. And as stated by the Federal Circuit, prior art references "must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention." *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986) (citing *W.L. Gore & Assocs. v. Garlock*, 721 F.2d 1540, 1550 (Fed. Cir. 1983)).

In the non-final Office Action mailed July 21, 2003, the Examiner stated: "Chu et al also teach that when Hib-HCH was injected with either Pn6A-HCH or Pn-TT [sic], both the anti-Hib and anti-Pn6A responses were increased over that induced by either conjugate alone." *See* non-final Office Action, p. 6, lines 12-14. These results are irrelevant to the claims of this application because they involve two different non-pneumococcal polysaccharide antigens (claim 1) and two different non-Dt non-Tt carrier proteins (claim 16). Furthermore, it is unclear whether the results are due to there being two different antigens or two different carrier proteins in the composition, or whether there was some other reason for the observed increase. One simply cannot make any conclusion with regard to this observation and the presently claimed invention. Moreover, if the results are due to there being two different carrier proteins, they contradict the results described above, where the Hib-HCH/Hib-TT combination was compared directly to either Hib-HCH or Hib-TT alone. Such contradictory evidence cannot rise to the level of suggesting the use of two carrier proteins as, at best, it only leaves the issue open for further investigation. Time and again the Federal Circuit has emphasized that obviousness under § 103 is not established by showing that the invention was "obvious to try." *See, e.g., In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

Furthermore, the Examiner has not pointed to any suggestion in EP '525 to modify the compositions taught therein to include more than one kind of carrier protein. There simply is no such suggestion in the reference; EP '525 consistently describes compositions containing a single carrier protein. Neither has the Examiner offered any reason whatsoever that one would have been motivated to modify the compositions taught by EP '525 to arrive at the composition recited in claim 1. Thus, neither Chu nor EP '525, alone or in combination, provides the requisite suggestion or motivation to combine and/or modify their respective teachings to arrive at the presently claimed compositions.

An examination of the problems sought to be solved by Chu and by EP '525 reveals why each reference fails to suggest or motivate one to make the composition recited in claim 1. Both Chu and EP '525 recognized that pure polysaccharides have limited use in vaccines because they do not produce a protective serum antibody response (*see, e.g.*, Chu at the paragraph bridging pp. 245-6). Accordingly, both research groups focused on the creation of new polysaccharide-carrier protein conjugates, including the development of new methods of making such conjugates, which elicit a stronger immune response than polysaccharide alone. However, neither Chu nor EP 0 497 525 noted the problem of "negative interference," which results when the immune response against a

polysaccharide decreases because the maximum load of carrier protein has been reached. For this reason, neither Chu nor EP 0 497 525 sought to solve the problem of "negative interference" by creating a polysaccharide vaccine composition containing more than one carrier protein, as the applicant has done. The Examiner's point that the simultaneous injection of two conjugates "did not exert a negative effect," as reported in Chu, is a red herring. See non-final office action mailed July 21, 2003, p. 6, lines 14-15; *see also* final office action mailed February 18, 2004, p. 2, last paragraph. The absence of a negative effect could have been observed simply because a low dose of conjugate was administered—not because two different carrier proteins were used. In other words, perhaps the dosage was too low to observe "negative interference" in any case—regardless of whether one or two carrier proteins were used.

Furthermore, the Examiner's presumption of a motivation to combine Chu and EP '525 neglects the essential fact that vaccines are usually administered to healthy people. There is hesitancy (rather than a motivation) to administer more than is necessary to a healthy person for fear of encountering unexpected adverse consequences. One would not combine antigens unless there is a reasonable expectation of achieving a beneficial result. And in the field of immunology it is recognized that a combination of antigens does not necessarily result in a cumulative (let alone synergistic) response. Because of the phenomenon of antigenic competition, whereby a combination of antigens results in a decreased immune response, one would not necessarily have expected to achieve a beneficial result. Neither Chu nor EP '525 teaches or suggests an advantage of altering the compositions disclosed therein in any way; their compositions are already useful by themselves, as they are. In view of the hesitancy of those skilled in the art to add additional components to a vaccine composition and the lack of any clear teaching of the cited art that making the modifications necessary to arrive at the presently claimed compositions would provide any beneficial effect, the requisite motivation is absent.

Because neither Chu nor EP '525 contains any suggestion or motivation to modify the compositions disclosed therein or to combine teachings to arrive at the compositions recited in claims 1-15 and 24, the first element of a *prima facie* case of obviousness has not been established with respect to these claims. For this reason, the applicant respectfully requests withdrawal of the obviousness rejection of claims 1-15 and 24.

## B. Neither Chu nor EP '525, either separately or in combination, teaches or suggests the compositions recited in claims 16-23

Claim 16 recites a composition comprising two different kinds of polysaccharide-carrier protein conjugates that differ in their carrier protein component, wherein one carrier protein is diphtheria toxoid (Dt) and the other carrier protein is tetanus toxoid (Tt). Claims 16-23 are directly or indirectly dependent on claim 16, and therefore they also include these two claim elements. Chu fails to teach or suggest the second element (in particular, it fails to teach or suggest Dt as a carrier protein), while EP '525 fails to teach or suggest the first (at least two conjugates comprising different carrier proteins). To establish a *prima facie* case of obviousness, the Office must show some suggestion or motivation to combine the teachings of Chu and EP '525 to arrive at the composition recited in claim 16.

As noted above, the Office has not pointed to any suggestion in Chu to make any additional compositions comprising at least two different kinds of polysaccharide-protein conjugates, wherein the conjugates contain different carrier proteins—including those comprising Dt carrier protein, as recited in claim 16. Moreover, as was the case with claim 1, the Office has not shown that one of skill in the art would have been motivated to modify the composition taught by Chu to arrive at the composition recited in claim 16. Again, upon reading the negative results reported in Chu, one of skill in the art would have been discouraged from making any additional compositions comprising at least two different conjugates. *See* Chu at page 249, col. 2, lines 8-17.

As was the case with claim 1, the reasons offered by the Examiner in past office actions for why one would have been motivated to modify the compositions taught by Chu, thereby arriving at the composition recited in claim 16, are unpersuasive. For example, in the non-final office action mailed July 21, 2003, the Examiner stated: "it would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the protein Dt of Merck and Co Inc for the HCH in the Hib-HCH conjugate of Chu et al because Chu et al teach that a 'useful' carrier would be preferred in human use . . . ." *See* non-final office action, p. 8, lines 8-14. Even assuming that Dt is a "useful" carrier (it is not described as such in Chu), this argument completely ignores the point made above: the results reported by Chu discourage one from making any additional compositions comprising more than one carrier protein—regardless of whether Dt is one of the carrier proteins included in the composition.

Furthermore, as noted above with regard to claim 1, the Examiner has not pointed to any suggestion in EP '525 to modify the compositions taught therein to include more than one kind of carrier protein. Again, there simply is no such suggestion in the reference; EP '525 consistently describes compositions containing a single carrier protein. In addition, the Examiner has not offered any reason that one would have been motivated to modify the compositions taught by EP '525 to arrive at the composition recited in claim 16. EP '525 was cited simply as a secondary reference—one that merely describes the use of Dt in a *Streptococcus pneumoniae* vaccine composition.

Because neither Chu nor EP '525 contains any suggestion or motivation to modify the compositions disclosed therein or to combine teachings to arrive at the compositions recited in claims 16-23, the first element of a *prima facie* case of obviousness has not been established with respect to these claims. For this reason, the applicant respectfully requests withdrawal of the obviousness rejection of claims 16-23.

Respectfully submitted,

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## APPENDIX A

1. A composition comprising "n" conjugates C1 to Cn, wherein
   (a) each conjugate comprises
      (i) a polysaccharide S1 to Sn from a *Streptococcus pneumoniae* serotype/serogroup, respectively, and
      (ii) a carrier protein P1 to Pn, respectively;
   (b ) "n" is a number equal to or greater than 2;
   (c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and
   (d) the carrier proteins P1 to Pn are selected independently from a group consisting of "m" carrier proteins, wherein "m" is a number equal to or greater than 2;
   (e) provided that at least one of the carrier proteins P1 to Pn is different from the others.

2. The composition according to Claim 1, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

3. The composition according to Claim 2, in which the polysaccharides S1 to Sn are all different from each other.

4. The composition according to Claim 1 in which "n" is a number equal to or greater than 6.

5. The composition according to Claim 4, in which "n" is a number equal to or greater than 10.

6. The composition according to Claim 1 in which the carrier proteins P1 and Pn are independently selected from the group consisting of two carrier proteins.

7. The composition according to Claim 6, in which when "n" is an even number, "n"/2 carrier proteins P1 to Pn are a first protein and "n"/2 carrier proteins P1 to Pn are a second protein or when "n" is an odd number, ("n"+1)/2 carrier proteins P1 to Pn are a first protein and ("n"-1)/2 carrier proteins P1 to Pn are a second protein.

8. The composition according to Claim 1 in which at least one of the carrier proteins P1 to Pn is the diphtheria toxoid (Dt) and at least one of the carrier proteins P1 to Pn is the tetanux toxoid (Tt).

9. The composition according to Claim 8, in which the carrier proteins P1 to Pn are selected from the group consisting of Dt and Tt.

10. The composition of Claim 8 in a dosage form in which the quantity of Dt is less than or equal to 200µg/dose.

11. The composition of Claim 8 in a dosage form in which the quantity of Tt is less than or equal to 50µg/dose.

12. The composition according to Claim 1, which comprises 10 or 11 conjugates in which the polysaccharides S1 to Sn are all different from each other and are chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F of *S. pneumoniae*.

13. The composition according to Claim 12, which comprises 10 or 11 conjugates selected from:

- serotype 1 polysaccharide coupled to Tt or to Dt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt or to Dt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 7F polysaccharide coupled to Tt or to Dt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 19F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Tt.

14. The composition according to Claim 1 wherein n is 12 to 22 and the composition comprises 10 or 11 different polysaccharides S1 to Sn chosen from serotypes 1, 3, 4, 5, 6B, 7F, 9V,

14, 18C, 19F and 23F and in which conjugates having the same polysaccharide differ from each other in the carrier protein.

15. The composition according to Claim 14, which comprises:

- serotype 1 polysaccharide coupled to Tt;
- serotype 3 polysaccharide coupled to Dt;
- serotype 4 polysaccharide coupled to Tt;
- serotype 5 polysaccharide coupled to Tt;
- serotype 6B polysaccharide coupled to Dt;
- serotype 6B polysaccharide coupled to Tt;
- serotype 7F polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Tt;
- serotype 9V polysaccharide coupled to Dt;
- serotype 14 polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Dt;
- serotype 18C polysaccharide coupled to Tt;
- serotype 19F polysaccharide coupled to Tt;
- serotype 23F polysaccharide coupled to Tt; and
- serotype 23F polysaccharide coupled to Dt.

16. A dose of a composition that comprises "n" conjugates C1 to Cn, wherein

(a) each conjugate comprises

(i) a polysaccharide S1 to Sn, respectively, and

(ii) a carrier protein P1 to Pn, respectively;

(b) "n" is a number equal to or greater than 2;

(c) the polysaccharides S1 to Sn are identical or there are from 2 to "n" different polysaccharides; and

(d) the carrier proteins P1 to Pn are selected independently from a group consisting of diphtheria (Dt) and tetanus (Tt) toxoids;

(e) provided that at least one of the carrier proteins P1 to Pn is different from the others and the quantity of Dt is less than or equal to 200 µg/dose and the quantity of Tt is less than or equal to 50 µg/dose.

17. The composition according to Claim 16, in which the conjugates C1 to Cn are all different from each other either by their polysaccharide, by their carrier protein, or by their polysaccharide and their carrier protein.

18. The composition according to Claim 17, in which the polysaccharides Sl to Sn are all different from each other.

19. The composition according to Claim 16 in which "n" is a number equal or greater than 6.

20. The composition according to Claim 19 in which "n" is a number equal to or greater than 10.

21. The composition according to Claim 16 in which the polysaccharides S1 to Sn are of bacterial origin.

22. The composition according to Claim 21 in which the polysaccharides S1 to Sn are all derived from the same bacterial species.

23. The composition according to Claim 22 in which the polysaccharides S1 to Sn are all derived from the species *Streptococcus pneumoniae*.

24. The composition according to Claim 14 that comprises 12 to 15 conjugates.